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Literatur Review

The level of effectiveness use of Quinoline Drugs in COVID-19

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Abstract

Chloroquine is the first line of medicine in the treatment of malaria. Besides being antimalaria, the chloroquine also can be used as the anti-inflammation in the medicine of arthritis rheumatoid arthritis and lupus erythematosus discoid. Hydroxychloroquine sulfate is 4-aminoquinolin with hydroxylated chloroquine analog, having the same pharmacokinetic as chloroquine which is given orally in hydroxychloroquine sulfate form, processed by gastro-intestinal absorption and very faster kidney elimination. The effectiveness of chloroquine and hydroxychloroquine towards COVID-19 in the in vitro experiment showed it could inhibit the duplication of the SARS-CoV-2 virus. The chloroquine function is to stop COVID-19 infection with (EC50) 1,13 µM and (CC50) larger than 100 µM. Meanwhile, the hydroxychloroquine function is to inhibit the attachment and entry of the virus into the host's cell by enzymatic activation which is the lysosome acidification disorder and antigen presentation as the result of pH increase. Based on the clinical study, the 10 of 12 patients who have lopinavir/ritonavir therapy by virology, the chloroquine group showed RT-PCR negative on day 7, 10, and 14 in compare to lopinavir/ritonavir that showed RT-PCR negative on day 14. On the 9th day, 60% of the patients of chloroquine group showed the CT scan of Lungs image normal instead of the lopinavir/ritonavir at 25%. In the day 14 based on the CT test result, the pulmonary improvement increased twice rather than chloroquine group (Rate Ratio 2.21). Meanwhile, the result of the study on the hydroxychloroquine and *azithromycin* combination use showed a decrease in viral load of 83% and 93% in tests with negative results in the day 7 and 8. It proved that the chloroquine role showed the result of the medicine has a significant effect by cleaning the virus or other clinical matters. The purpose of this literature review is to know the effectiveness quinoline class of drugs which is chloroquine and hydroxychloroquine in COVID-19 disease.

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INTRODUCTION

The COVID-19 pandemic started in China last December 2019 located in Wuhan. In an attempt to stop the spread, in January 2020, this virus had spread widely in Asia country, and the first identification case of the virus's spread was in Europe. Initially, this disease named a 2019 novel coronavirus (2019-nCoV). On February 11 2020, WHO officially named this disease as Coronavirus Disease 2019 (COVID-19) that is caused by a novel coronavirus. Moreover, Coronavirus is a new disease for the people that became a big threat in a large society (WHO, 2020).

There is some accepted medicine by FDA as the COVID-19 therapy, such as ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, and two antiviruses broad-spectrum medicine redeliver and favipiravir to the clinical symptoms of COVID-19 by in vitro. Among the seven medicines it was found a high concentrate test from three nucleoside analog which is ribavirin (EC50 = 109,50Mm), penciclovir (EC50 = 95,96 µM), favipiravir (EC50 = 61,88 µM), nafamostat (EC50 = 22,50 µM), nitazoxanide micromolar (EC50 = 2,12µM), remdesivir micromolar (EC50 = 0,77µM), and chloroquine (EC90 = 6,90µM).

The chloroquine and 4-aminoquinoline hydroxychloroquine are the quinoline family that has the same molecule. The hydroxychloroquine is different from chloroquine because of the hydroxyl group existence at the end of the substituent side-chain N-ethyl βhidroksilasi (Devaux et al., 2020). Chloroquine itself is distributed all over the body including lungs after given orally. The chloroquine and hydroxychloroquine function are known to block the virus infection by increasing the pH endosome which is needed for the fusion of virus/cell also disturbing the glycosylation cellular receptor of SARS-CoV-2 (Wang et al., 2020).

The use of chloroquine itself must be based on the rules and not for self-medication. Generally, the phosphate chloroquine and hydroxychloroquine are commercialized as the antimalaria medicine that is used in an autoimmune disease like lupus and rheumatoid arthritis. There is a special consideration in using chloroquine and hydroxychloroquine that is considered safe and mild side effects so can consider the use of chloroquine and hydroxychloroquine dose margin therapy to avoid chloroquine poisoning and not cause cardiovascular disorder complication that can be life-threatening (Touret & Lamballerie, 2020).

METHODS

The method used is by collecting and analyzing the articles related to the effectiveness of quinoline drugs which is chloroquine and hydroxychloroquine in COVID-19 disease. The articles were obtained by using an electronic database searching from Google Scholar, PubMed, and Elsevier using the keywords Effectiveness, Quinoline, Chloroquine, Hydroxychloroquine, and COVID-19. The reviewed articles are from the year 2010-2020 that discussing COVID-19, in full-text format, that specifically discusses the effectiveness of quinoline drugs which is chloroquine and hydroxychloroquine in COVID-19 disease.

COVID-19 DISEASE

Coronavirus is a beta coronavirus that has RNA single strand genome and helical capsid with envelopes that consisted of lipid bilayer diameter 60-100nm. The sequence analysis of the COVID-19 genome showed that it has substantial similarity as Coronavirus like SARS, which mostly infected bats, which later mutate and infect humans (Frater et al., 2020). Coronavirus is one of the diseases that the spread of infection is very fast through the respiratory tract, so that can affect the syndrome of symptoms acute breathing because of SARS-

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CoV-2 (Rothan & Byrareddy, 2020). The incubation period is 2-14 days until the patient showed symptoms, including fever (99%), cough (50%), and breathing difficulty (33%) as the most common complaint. Mostly, about 80% of infected people have mild to moderate symptoms, and the rest are quite severe (WHO, 2020). The COVID-19 patient with respiratory tract medical records tend to have more severe clinical manifestations (Yang et al., 2020). The Centers for Disease Control and Prevention (CDC) announced some other risk factors that can cause the COVID-19 infection starting from the highest to lowest, having close contact to COVID-19 patient, being in the same environment but no contact, and arriving from infected country history (CDC, 2020).

Based on the data and study cases result, it showed that age, gender, active smoker, and having a comorbid disease such as diabetes mellitus and hypertension are the risk factors of SARS-CoV-2 infection. The elderly are more susceptible to SARS-CoV-2 since they have higher possibility frequency related to the comorbid disease. Males have a higher prevalence rather than females, and it was predicted to associate with a higher tendency of an active smoker. The SARS-CoV-2 infection will be related to their target cell through angiotensin-converting enzyme 2 (ACE2), which is expressed by epistle pulmonary cells, kidney, and blood vessels. As to the smoker, hypertension, and diabetes mellitus, it was predicted that there is an increased receptor expression of ACE 2. (Cai, 2020).

Pathogenesis COVID-19

ACE2 is a protein-membrane type I which facilitates the virus attachment to a cellular receptor, initiation infection, and angiotensin-converting enzyme 2 (ACE2) that is expressed to lungs, heart, kidney, and intestine so it can be identified as a functional cellular receptor of SARS-CoV-2. (Jin et al., 2020). Based on his analysis, Zhao showed that angiotensin-converting enzyme 2 (ACE2) is the receptor for SARS-CoV-2. In the lungs of normal people, ACE2 is expressed to the epistle cell of alveolar I and II. The relation of SARS-CoV-2 to ACE2 causes an expression increase of ACE2 that can cause alveolar cell damage. The damage of alveolar cells can trigger some systematical reactions and even mortality (Sun et al., 2020). The first clinical description showed by the infected people through the COVID-19 pandemic is respiratory symptoms. The spread of COVID-19 from humans to humans becomes the main transmission source so the spread becomes more aggressive. The transmission of SARS-CoV-2 happened through droplet that comes out from the cough or sneezing (Han & Yang, 2020).

Chloroquine

Chloroquine is prophylaxis drugs formed amine acidotropic of quinine and hydroxychloroquine that mostly used as malaria drugs before. Based on in vitro study, the chloroquine function is to block COVID-19 infection in low micromolar concentration by the effective concentration of half the maximum (EC50) 1,13 µM and 50% cytotoxic concentration (CC50) larger than 100 µM (Gao et al., 2020). From its pharmacokinetics travel of chloroquine, it is given orally in a tablet in the form of phosphoric acid. The chloroquine in metabolism becomes the active metabolite and desethyl chloroquine through cytochrome liver enzymes P450 (CYP) 2C8 and CYP3A4. The mechanism of chloroquine is distributed widely in most organ systems including eyes, heart, liver, lungs, and last secreted through the kidney. In COVID-19 medication based on the expert's study, they suggested to use phosphate chloroquine tablet by dosage 500mg per oral twice or in 10 days (Barlow et al., 2020) and from pharmacodynamics mechanism, the

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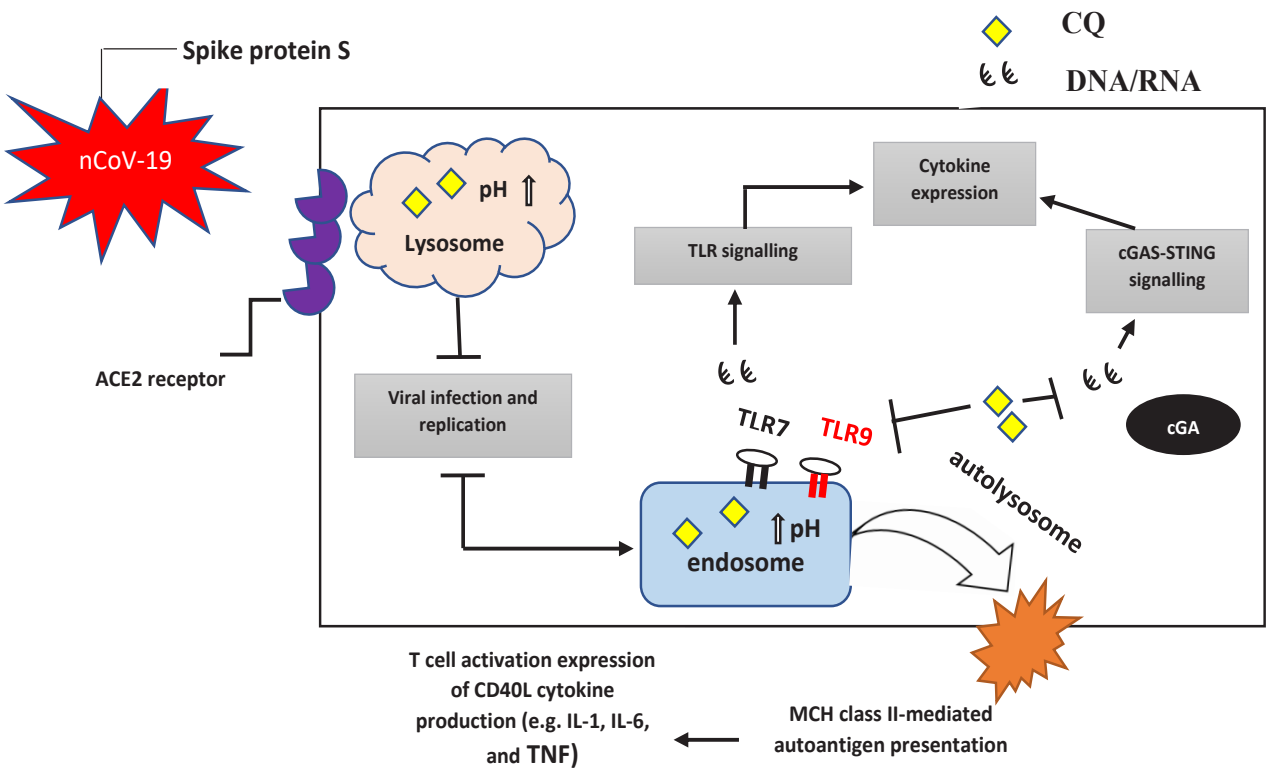

Figure 1. Mechanism of chloroquine towards COVID-19

chloroquine drugs work to change glycosylation by increasing pH intracellular vacuole level and change the protein degradation track through acid hydrolase in lysosomes, macromolecule synthesis in the endosome, and protein modification of post-translation in Golgi body so there is an antigen macrophage activation in reaching antirheumatic response that can disturb a process of antigen (Sahraei et al., 2020)

The base chloroquine works by penetrating cells that acid concentrated so cause an increase of pH endosome. This condition can be the potential therapeutic strategy to virus infection that can inhibit the production of some cytokine, chemokine, or mediator that exaggerated in contributing to the virus infection severity (Vincent et al., 2005). Moreover, the chloroquine can set the immune system by influencing cell signal and cytokine proinflammation production (Zhang et al., 2020). In orderly, the chloroquine non-protonated entering cells by concentrating on acid organelle becomes protonated, the low pH like endosome, Golgi vesicles, and lysosome. The chloroquine can work effectively in influencing virus based on their amount by using endosome as the mediator of virus duplication (Al-Bari, 2017). The indication of chloroquine use for prophylaxis malaria treatment is sensitive to chloroquine (P. falciparum, P. Ovalle, P. Vivax, and P. malaria) and as extraintestinal amebiasis treatment. Meanwhile, the Covid-19 treatment is given to people who indicate an Acute Respiratory Distress Syndrome (ARDS) symptoms such as asphyxiated and breathing difficulty. Besides, the chloroquine contraindicated cannot be used to the patient with retinal disorder or insight except for acute malaria treatment, 4-*aminoquinoline* hypersensitivity, and QT interval extension. The drug administration of chloroquine can be given to prophylaxis for malaria orally with the dose 500mg two weeks before, during, and 8 weeks after exposure to endemic areas. In amebiasis, the drugs given

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orally in the dose 21mg/kg during 3 weeks and for severe malaria treatment can be given parenterally or subcutaneous (Goel & Gerriets, 2019).

The use of chloroquine suggested for an adult is consist of 600 mg base chloroquine (6 tablets CQ 100 mg) followed by 300 mg after 12 hours on the day 1, then 300 mg (2x a day) on the 2-5 day, and 500 mg (2x a day) (Cortegiani et al., 2020). The side effects of chloroquine consumers are nausea, vomit, stomachache, diarrhea, cough, shortness of breath, and rash or itchy (Huang et al., 2020). The monitoring that can be conducted when using chloroquine is including initial electrocardiogram (ECG), electrolyte, kidney function, and liver test.

Some complications might happen in using chloroquine that can make QT extension with insufficient or kidney failure, increasing the insulin level that can cause severe hypoglycemia, caused hemolysis to the patient with glucose-6-phosphate dehydrogenase (G6PD), even interacting with other drugs can risk the QT extension even after have stopped the drugs in a long time about 30-60 days (FDA, 2020).

Hydroxychloroquine

Hydroxychloroquine sulfate is 4-aminoquinolin as chloroquine analog which is hydroxylated. Generally, this drug mostly the same as chloroquine which is used as the antimalaria drug. This drug role is inhibiting plasmodial polymerase.

Some analysis result mentioned that hydroxychloroquine can heal varied condition such as diabetes mellitus, dyslipidemia, coagulopathy, infectious diseases, malignancy, and some autoimmune disease, arthritis rheumatoid, and Systemic Lupus Erythematosus (SLE) (Ponticelli & Moroni, 2017).

Hydroxychloroquine has the same pharmacokinetic with chloroquine which is given orally in hydroxychloroquine sulfate form, by the absorption gastrointestinal process, and faster kidney elimination (Devaux et al., 2020). Besides being antimalaria, hydroxychloroquine also has some mechanism effects of antiinflammation such as lysosome

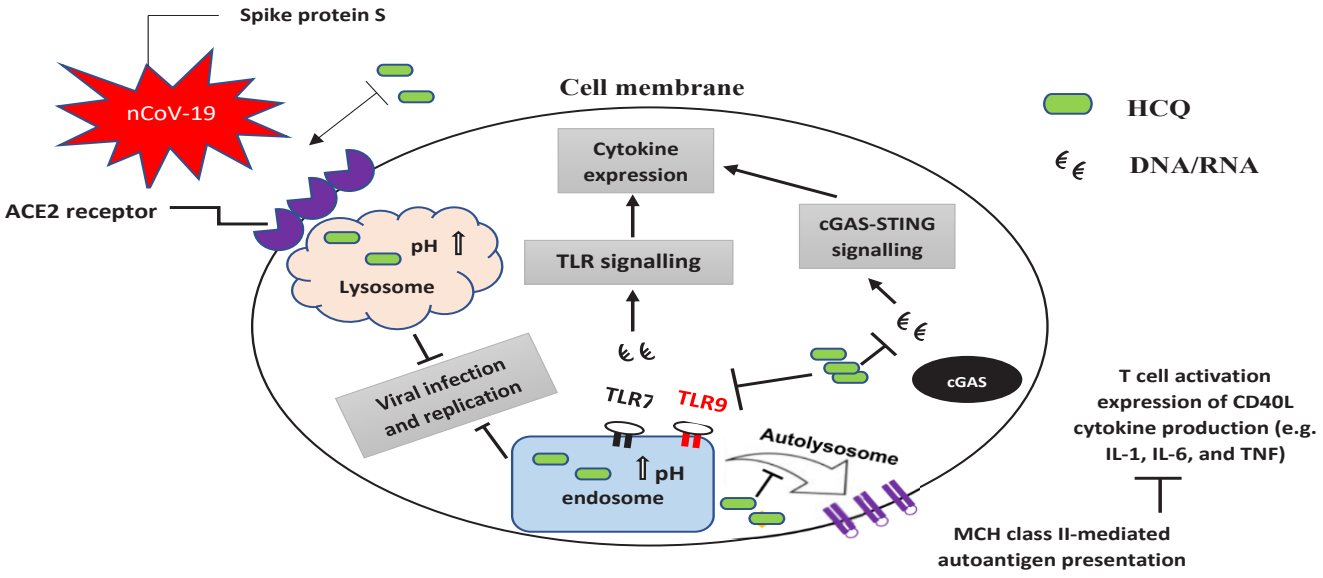

Figure 2. Mechanism of hydroxychloroquine towards COVID-19

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acidification disorder and antigen presentation, A2 phospholipase absorption inhibitor, absorption and blocker of UV skin reaction, binding and stabilizing DNA, TLR signal inhibitor, calcium T cell receptors inhibitor, and decreasing cytokine production which using macrophage media such as interleukin IL-1 and IL-6. The interaction between TLR and cell receptors can cause hydroxychloroquine more effective in some flow signal locations as the response of inflammation (Sinha & Balayla 2020).

Furthermore, it also has an anti-virus effect mechanism effect that is hydroxychloroquine inhibits and attaches the virus entry to the host's cell. This proofed to decrease Phosphatidylinositol Binding Clathrin Assembly Protein (PICALM) so it can arrange the cellular endocytosis rate which is mediated by Clathrin-Mediated Endocytosis (CME) as the mediator that has a role when SARS-CoV-2 entering human's cell. Next, S protein from Coronavirus will undergo proteolytic that based on endosomal protease acid cellular, for example, cathepsin or Transmembrane Serine Protease 2 (TMPRSS2).

In the process of cleavage resulting membrane endosome virus fusion that can be inhibited by pH increase. The process is the enzymatic activation phase from both cathepsin and TMPRSS2 which have an effect in virus attachment, entering the host cell, and block the virus inside endocytic vesicles. The mechanical effect of another antivirus is the inhibition of maturation and the spread of a new virus particle. In this phase, the hydroxychloroquine acts as endosomal alkalization, inhibits or prevents endosome-lysosome membrane fusion that leads to recycling viral membrane receptor process, the virus release, and virus genome inside the cytosol of SARS-CoV-2 virus (Quiros Roldan et al., 2020).

The indication of hydroxychloroquine use is to treat autoimmune diseases such as Systematic Lupus Erythematosus (SLE) and rheumatoid arthritis and also use to prevent and medicine of malaria. Meanwhile, the Covid-19 treatment is given to people who indicate an Acute Respiratory Distress Syndrome (ARDS) symptoms such as asphyxiated and breathing difficulty (Meyerowitz et al., 2020). The contraindication of hydroxychloroquine use is on retina disorder or retinopathy, cardiomyopathy, Long QT Syndrome, psoriasis arthritis, porphyria, and neuropathy (Pastick et al. 2020).

The dosage given is 3x200mg hydroxychloroquine for 10 days but the treatment can be varied from 5 to 20 days based on the clinical level especially in respiratory disorder (Cortegiani et al., 2020). The side effect of hydroxychloroquine can appear as gastrointestinal symptoms such as nausea, vomit, unusual shortness of breath, cardiotoxicity that leads to QT abnormalities (Hashem et al., 2020). The possible monitoring in using hydroxychloroquine is hematology parameter (RBC, WBC, and thrombosis amount), measuring electrolyte serum, blood glucose, and liver and kidney function (Singh et al., 2020).

The Effectiveness of chloroquine and hydroxychloroquine in COVID-19

Recently, the specific anti-virus treatment is not found yet for COVID-19. However, the effective supportive treatment still being an urgent need as the temporary treatment to decrease a mild or medium clinical symptoms up to 5-10% and potentially life-threatening weight of COVID-19 is chloroquine/hydroxychloroquine, remdesivir, and lopinavir-ritonavir (Şimşek Yavuz & Ünal, 2020).

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supportive treatment still being an urgent need as the temporary treatment to decrease mild or moderate clinical symptoms up to 5-10% and potentially life-threatening weight of COVID-19 is chloroquine/hydroxychloroquine, remdesivir, and lopinavir-ritonavir (Şimşek Yavuz & Ünal, 2020).

Chloroquine is anti-malaria drugs which are mostly used as the immunomodulatory effect meanwhile hydroxychloroquine based on the past study mentioned that can treat SARS plague. It is proofed that medicine has an activity of anti-SARS-CoV by in vitro. But until recent days, there is no clinical proof that shows if hydroxychloroquine can treat SARS-CoV-2 (Yao et al., 2020). On the other way, there are some studies that stated that chloroquine has cytotoxic concentration 50% (CC50). It proofed that the chloroquine activity is very selective in fighting virus duplication from the host's cell (Liu et al., 2020).

By in vitro, chloroquine and hydroxychloroquine 4-aminoquinolin are a low base that increases the endosomal pH of the host's intracellular organelle that can inhibit autophagosome-lysosome fusion and non-activated the enzyme needed by the virus to duplicate. The role of COVID-19 can affect the glocalization of angiotensin-converting enzyme-2 (A2) so it comes to the result that can inhibit SARS-CoV-2. More than 100 patients showed that phosphate chloroquine is more effective in inhibiting exacerbation (Ferner & Aronson, 2020).

Besides, the chloroquine has a function in modulating the immune system activity that synergistically increases the antivirus effect by in vitro. It proofed that by in vitro, the chloroquine is very effective in controlling COVID-19 infection. There is some proof that has been conducted in China for the COVID-19 patient who consumes chloroquine orally that is distributed to lungs and all over the body and have evidence of clinical achievement (EC50) 6,90 μM in Vero E6 that is gained by patient's plasm of rheumatoid arthritis in the dose of drugs 500 mg (Wang et al., 2020).

Based on the National Health Commission of the PRC study result, the chloroquine is used back as the emergency therapy of COVID-19 treatment. There are 82 patients who are screened COVID-19 test and 22 of them showed positive criteria of SARS-CoV-2 after conducted the RT-PCR test. the confirmed 22 patients are mixed into two first groups 10 people treated by using chloroquine 500 mg per oral two twice a day, including the 3 patients of severe level and 7 patients of moderate level. Next, in the second group of 12 people treated by lopinavir/ ritonavir 400/100 mg per day for 10 days, including 5 patients of severe level and 7 patients of moderate level. The level of effectiveness in the chloroquine group showed that 1 people is negative after 2 days of treatment. It shows that chloroquine experienced earlier development

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Table 1. Clinical study of chloroquine in COVID-19 patient

82 patient (n=22)	Patient	Clinical Status	Treatment	Duration	Percentage
1.	10 patients	3 severe 7 moderate	Chloroquine 2x500 mg/day per oral	14 days	60 % pulmonary improvement
2.	12 patients	5 severe 7 moderate	Lopinavir/ritonavir 400/100 mg/day	10 days	25 % pulmonary improvement

Table 2. Clinical study of hydroxychloroquine in COVID-19 patient

	Researcher	Patient	Group Control	Treatment	Duration	Improvement Percentage
1.	Gautret et al	20 patients	16 patients	Hydroxychloroquine 200 mg/8 hour or azithromycin 500 mg/first day and 250 mg/2-5 days after	10 days	17%
2.	Gautret et al	80 patients with Inclusive criteria and exclusive 69 out of 75	NO	Hydroxychloroquine 200 mg/8 hour and azithromycin 500 mg/first day and 250 mg/2-5 days after	10 days	93%
3.	Chen et al	30 patients	15 patients	Hydroxychloroquine 200 mg/12 hour	7 days	86,7%
4.	Chen et al	62 patients	31 patients	Hydroxychloroquine 200 mg/12 hour	5 days	80,6%
5.	Molina et al	11 patients	NO	Hydroxychloroquine 200 mg/8 hour and azithromycin 500 mg/first day and 250 mg/2-5 days after	10 days	57,1%

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from lopinavir/ritonavir treatment, and having an improvement on day 13 that accumulated as a patient with chloroquine treatment showed a negative result. Based on the clinical study, the 10 of 12 patients who have lopinavir/ritonavir therapy by virology, the chloroquine group showed RT-PCR negative on day 7, 10, and 14 in compare to lopinavir/ritonavir that showed RT-PCR negative on day 14. On the 9th day, 60% of the patients of chloroquine group showed the CT scan of Lungs image normal instead of the lopinavir/ritonavir at 25%. In the day 14 based on the CT test result, the pulmonary improvement increased twice rather than chloroquine group (Rate Ratio 2.21). This proved that the chloroquine treatment has better effectiveness in COVID-19 in stopping the virus duplication and repairing the pulmonary function faster (Huang et al., 2020).

The given clinical data of hydroxychloroquine in the first study is from Philippe Gautret by using 20 participants that consumed hydroxychloroquine and 6 of them also consumed azithromycin. About 16 patients are controlled under the short analytical observation for 6 days showed results in the intervention and control groups. 17% of patients did not show any symptoms and only 22% of them has pneumonia. The second study, even though it showed a bigger result but did not have a control group. Besides, inclusive and exclusive criteria showed that 69 of 75 patients or about 92% had a similar clinical result with the patient that had no COVID-19 treatment. The combination of hydroxychloroquine and azithromycin showed a decrease in the viral load of 83% and 93% tested with a negative result in day 7 and 8. Jun Chen's study of 30 patients found that there is no significant difference in the nasopharynx virus test on day 7 with local treatment standards. The second test of Zhaowei Chen in 62 patients of hydroxychloroquine treatment showed a clinical recovery in a short period of time such as temperature and cough. The last study in 11 patients showed the SARS-CoV-2 persistence in nasopharynx swab from 8 out of 10 patients that received hydroxychloroquine treatment (Taccone et al., 2020).

The Gautret et al. study result stated that China experts used chloroquine and hydroxychloroquine in giving COVID-19 patient clinical treatment. It is because the role of chloroquine and hydroxychloroquine towards the growth of SARS-CoV-2 is by in vitro, showed a result that chloroquine has a significant effect in inhibiting the virus duplication or even the clinical matters. Moreover, in chloroquine treatment mentioned, the experts suggested that the patients diagnosed as pneumonia COVID-19 in the degree of mild, moderate, and severe without contradiction to chloroquine can be treated with the dose 2x500 mg for 10 days (Gautret et al., 2020).

The chloroquine and hydroxychloroquine have as similarity in increasing intracellular acid organelles pH such as endosome or lysosome fusion mechanism membrane. The chloroquine function is to inhibit the SARS-CoV-2 entry so there will no protein improvement by glycosylation receptor process ACE2. Meanwhile, the hydroxychloroquine is effective in inhibiting the entry of SARS-CoV-2 and post-event after SARS-CoV-2 entry. Both of them can be differentiated by the cytotoxic level that showed hydroxychloroquine lower than 40% than chloroquine (Liu et al., 2020). There are some studies about the difference in effectiveness between chloroquine and hydroxychloroquine. Based on Yao et al., he tested the antivirus in the Vero cell line that is infected by SARS-CoV-2. The result is hydroxychloroquine is more effective in disturbing virus duplication instead of chloroquine that is given after the infection with EC50 in 48 hours each 0,72μM and 5,47μM for hydroxychloroquine and chloroquine after given prophylaxis EC50 in 48 hours that is 5,85 μM dan 18,01 μM. Besides, based on Liu

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et al., mentioned that chloroquine is stronger that hydroxychloroquine in waiting for the virus duplication based on the E6 Vero test in African green monkey's kidney and resulted in CC50 of chloroquine and hydroxychloroquine is 273.20 µM and 249.50 µM. But, both of them are known can inhibit the SARS-CoV-2 virus duplication (Pastick et al., 2020).

CONCLUSION

The Coronavirus is one of the diseases in which its infection spread is very fast which is through the respiratory tract so that it can cause a syndrome of symptoms acute breathing. The genome similarity between SARS-CoV-2 and SARS-CoV becomes strong proof that SARS-CoV-2 comes from the bats. By in vitro, chloroquine and hydroxychloroquine from 4-aminoquinolin is very effective in controlling the COVID-19 infection that has a function in inhibiting enzyme needed by the virus to duplicate themselves. The chloroquine treatment can be given to the patient who is diagnosed as pneumonia COVID-19 in the degree of mild, moderate, and severe without any contraindication towards chloroquine dose is 3x200 mg in 10 days but the treatment can be varied from 5 to 20 days based on the clinical degree especially in respiratory disorder.

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